FORMULATION DEVELOPMENT, OPTIMIZATION, AND EVALUATION OF A DRUG PRODUCT WITH A POORLY WATER-SOLUBLE TYROSINE KINASE INHIBITOR

SYNOPSIS

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INTRODUCTION

Drug development is a major field in research and development in pharmaceutical sciences that constantly faces a lot of issues and is responsible for solving the issues pertaining to this field. The most common problems are the low bioavailability, palatability, first pass metabolism, difficulties in administration of drugs, dose precision, dose requirement and ease of administration of the drug (Niazi *et al.*, 2019).

The major factors responsible for the low bioavailability of a drug is its solubility and permeability. Based on these two factors, the molecules are classified into four groups according to the Biopharmaceutical Classification System. The four groups respectively are: Class I (high solubility and high permeability), Class II (low solubility and high permeability), Class III (high solubility and low permeability), and Class IV (low solubility and low permeability) (Gurunath *et al.*, 2013; Salmani *et al.*, 2014). Class II and Class IV have low solubility and researchers are inclined to research. Researchers are continuously working on these two classes to improve their bioavailability in order to produce a better and effective drug product (Mohammed & Ghareeb, 2018).

Solubility Enhancement Techniques: Few techniques which are commonly used for solubility enhancement are mentioned below.

i. Chemical modifications

- Salt formation
- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilizing agent
- Nanotechnology

ii. Physical modifications

- Particle size reduction
- Modification in crystal forms
- Complexation

- Solid dispersion
- Addition of surfactants

iii. Miscellaneous

- Supercritical fluid technology
- Lyophilization or freeze-drying
- Evaporative precipitation
- Electrostatic spinning method
- Polymeric alteration
- Inclusion complexes
- High-pressure homogenization

Renal cell carcinoma contributes about 2-3% of all cancer with maximum occurrence in the western countries (Psimadas *et al.*, 2012). Renal cell carcinoma (RCC) is commonly encountered in the practice of nephrology, particularly when acute kidney injury (AKI) or chronic kidney disease (CKD) develops in patients with RCC or when a mass is incidentally discovered during workup of kidney disease (Thurnher *et al.*, 2008). Importantly, RCC is a disease of increasing incidence, which is in part related to more sensitive imaging modalities (Psimadas *et al.*, 2012b). Clear cell RCC, the focus of this review, is the most common histological subtype (Barata & Rini, 2017). Other less common kidney cancers include papillary, chromophobe, and other rare tumors of the nephron and collecting system and are not discussed here.

LITERATURE REVIEW

Solubility is characterized as the sum of substance that passes into the solution to form a saturated solution at steady temperature and pressure. Solubility can be framed in terms of the maximum volume or mass of the solute that breaks up in a given volume or mass of a solvent. It can be expressed as the ability of substance A to form a solution with substance B (Salmani *et al.*, 2014). Solid dispersion (SD) is an emerging method and is being continuously explored. It is used to increase the solubility of poorly soluble drugs. Solid dispersion can be defined as the dispersion of a hydrophobic drug molecule in a hydrophilic carrier (Baghel, Cathcart & O'Reilly, 2016). One or more active pharmaceutical ingredients (API, or drug molecule) in dispersed in an inert carrier or matrix at a solid state. Solid Dispersions can be prepared using different methods such as

melting (fusion) (Fan, Zhu & Di, 2019), solvent evaporation, (Sethia & Squillante, 2004) and melting-solvent method (Emara, Abdelfattah & Taha, 2017).

Classification of Solid Dispersion: Solid dispersion can be classified on the basis of carrier used and molecular arrangement. On basis of the carrier used solid dispersion can be classified as (Mishra et al., 2015):

1. First-generation Solid Dispersion
2. Second generation Solid Dispersion
3. Third generation Solid Dispersion
4. Fourth-generation Solid Dispersion

First generation	**Second generation**	**Third generation**	**Fourth generation**
Crystalline in nature	Amorphous carriers, which are mostly polymers. Can be classified into amorphous solid solutions (glass solutions) and amorphous solid suspensions.	Surface active agents or self-emulsifiers.	Controlled release pattern. Used for poorly water-soluble drugs with a short biological half-life.
Carrier: Urea and sugars such as sorbitol and mannitol.	Carrier: Povidone (PVP), polyethyleneglycols (PEG), polymethacrylates, hydroxylpropylmethyl-cellulose (HPMC), ethyl cellulose, hydroxypropylcellulose, and cyclodextrins.	Carrier: Inulin, Inutec SP1, Compritol 888 ATO, Gelucire 44/14 and Poloxamer 407.	Carrier: Hydroxypropylmethyl cellulose (HPMC), Poly (vinyl pyrrolidone/vinyl acetate co polymer) (PVP), Polyacrylates, Hydroxypropylmethyl cellulose acetate/succinate (HPMC AS), and Polymethacrylates.

On basis of molecular arrangement solid dispersion can be classified as (Tran *et al.*, 2019)**:**

1. Eutectic mixtures
2. Amorphous precipitation in a crystalline carrier
3. Glass solution
4. Solid Solution

Eutectics Systems	**Amorphous precipitation in a crystalline carrier**	**Glass solutions and suspensions**	**Solid Solutions**
Consist of two compounds which in the liquid state are completely miscible but in the solid-state only to a very limited extent. By rapid solidification of the fused melt of two components these are prepared and that show complete liquid miscibility and minor solid-solid solubility	In the crystalline carrier, the drug may also precipitate in an amorphous form instead of simultaneous crystallization of the drug and the carrier (eutectic system). The amorphous solid state.	Glass suspensions are mixtures in which precipitated particles are suspended in glass solvent. Examples of carriers that form glass solutions and suspensions are citric acid, PVP, urea, PEG, sugars such as dextrose, sucrose, and galactose.	In this system, a homogeneous one-phase system is formed when the two components crystallize together. The particle size of the drug is reduced to its molecular size in the solid solution. Solid solutions can be classified as continuous or discontinuous according to the extent of miscibility of the two components.

Advantages of Solid Dispersion (Van Den Mooter, 2012)

- Enhances solubility and bioavailability of poorly water- soluble drugs.
- Easier to produce and is more applicable.
- Leads to an increase in the extent and rate absorption of a drug.
- Transformation of the liquid form of drug into a solid form.
- Control of various parameters like molecular weight, composition, particle porosity, and wettability can enhance the bioavailability of poorly water-soluble drugs.
- Easier production of rapid disintegration oral tablets by solid dispersion.
- Taste masking
- Improved porosity.

Disadvantage of Solid Dispersion (Huang & Dai, 2014)

- Poor scale-up for manufacturing.
- Polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth, and convert the amorphous form into crystalline form.
- Laborious method of preparation.
- Reproducibility of physicochemical characteristics.

Techniques for Solid Dispersions (Van Den Mooter, 2012)

- Solvent evaporation
- Hot-melt extrusion
- Fusion method
- Solvent melt method
- Kneading technique
- Adsorption on insoluble carriers/fluidized bed system
- Melt agglomeration method
- Dropping method

Methods to enhance solubility:

1) **Micronization:** As the drug belongs to BCS class II, the drug has low solubility and high permeability. Micronization is one of the best way to enhance the drug solubility. Micronization is a conventional technique for the particle size reduction. Micronization increases the dissolution

rate of drugs through increased surface area, it does not increase equilibrium solubility (Tran *et al.*, 2019). Decreasing the particle size of these drugs, which cause increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug (Figure 1).

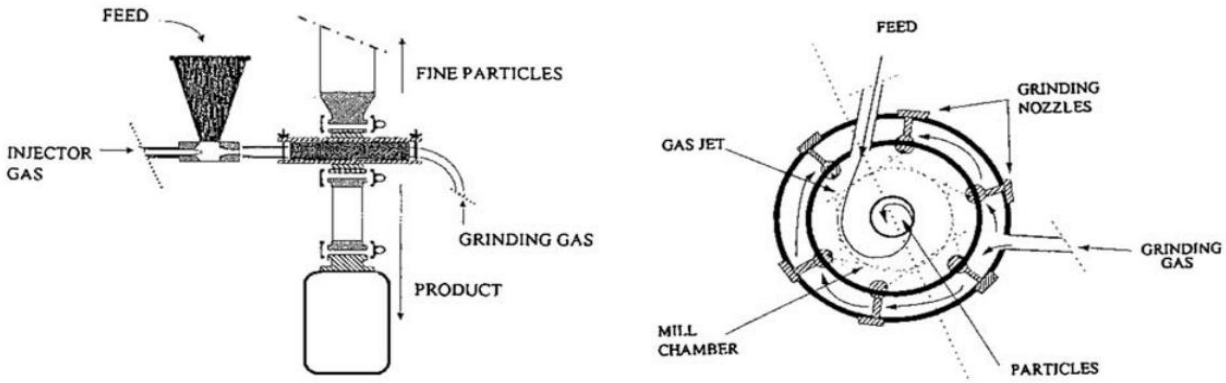

Figure 1: Diagrammatic representation of milling process.

2) **Hot melt extrusion technique:** Hot-melt extrusion (HME) is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of the drug and the matrix could be a problem. High-shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding (Alshehri, 2015).

   Extrusion is the process of changing the physical properties of the substance by forcing it through an orifice or die under controlled conditions (Factor *et al.*, 2015). HME is an innovative and efficient technology for manufacturing different dosage forms and drug delivery systems in the pharmaceutical industry. HME is a green synthesis technique as it avoids the use of organic solvents showing maximum scalability using the process. Researchers have been working on pellet formulations of different drugs using HME (Roychowdhury, Kara & Rathnanand, 2021).

   Components of the hot melt extrusion process: feeding, metering, and melting. The rotating screws force the feed material forward towards the die, and the material is softened by the frictional heat developed through the barrel wall. The feed reaches the end of the screw in a viscous state that can

then be forced through an orifice (or die) and molded into the desired shape (Maniruzzaman *et al.*, 2012).

The extrusion equipment is classified into three main categories: ram, radial screen, and roll and screw extruders. Types of Screw Extruders:

- Single-screw extruders (SSEs): smooth or grooved barrel.
- Twin-screw extruders (TSEs): co-rotating or counter-rotating with intermeshing or non-intermeshing screws.
- Multi-screw extruders (MSEs): static or rotating central shaft (Patil, Tiwari and Repka, 2016).

Amorphization of a drug increases the solubility of the drug because of increased surface area and better ability of the solvent to wet the drug. Such a process can improve the bioavailability of poorly soluble drugs, namely, BCS class II and BCS class IV drugs (Enose *et al.*, 2014). The drug-polymer is melted above its glass transition temperature to form a glassy state and is suddenly cooled forming a dispersion where the drug is in the super-cooled liquid state, or frozen glassy state. The amorphous state of a drug has a higher enthalpy, free energy, and volume as compared with the crystalline form which is responsible for its higher apparent solubility (Baghel, Cathcart & O'Reilly, 2016).

Major concerns with the development of Solid dispersion are the choice of method and the stability of the formulation. The processing of an API with a specific method (fusion method) from a thermodynamic point of view. The involvement of complex processes like HME raises the risks of re-crystallization and stability issues (Schittny, Huwyler & Puchkov, 2020) (Figure 2).

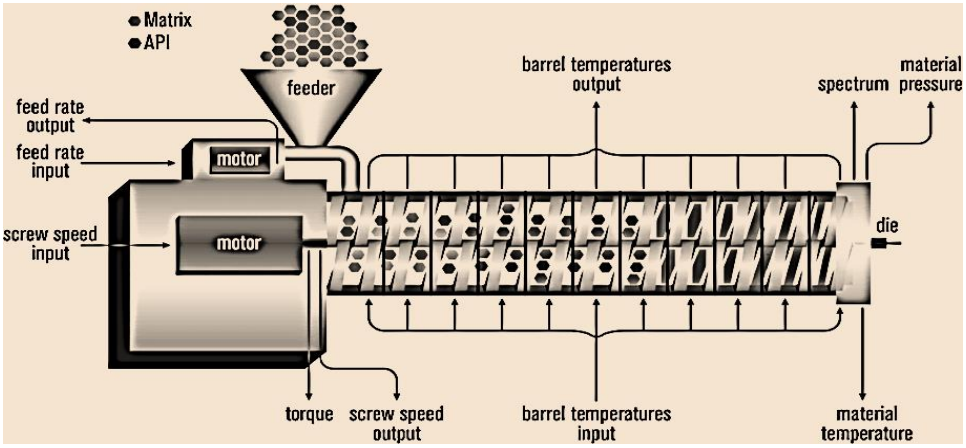

Figure 2: Diagrammatic representation of HME.

3) **Spray drying:** Spray drying is a very widely applied technique used to dry aqueous or organic solutions, suspensions and emulsions in the food, chemical, electronics, pharmaceutical and biopharmaceutical industry. Within the food industry spray drying is used to prepare a wide range of products, e.g. baby and infant food, instant coffee, dried milk products, tomato paste. The chemical industry applies spray drying to manufacture aluminum chlorohydrate, ammonium nitrate, ammonium phosphate, magnesium hydroxide, zinc oxide, zinc sulphate, bleach powders, carbides (titanium, silicon, tantalum, niobium), catalysts for inorganic and organic chemical reactions, ceramic metals, detergents, dyestuffs, pigments. Electrical insulating material consists of spray dried aluminum oxide. Within pharmaceutical and biopharmaceutical industry spray drying is often selected to transform the active pharmaceutical ingredients in a powder and to manufacture solid dosage forms containing peptides, proteins or poorly water soluble active pharmaceutical ingredients (Enose *et al.*, 2016). For example, antibiotics such as ampicillin, auremycin, penicillin, streptomycin, terramycin and tetracycline are spray dried, despite some activity loss (2–10%) during processing (Figure 3).

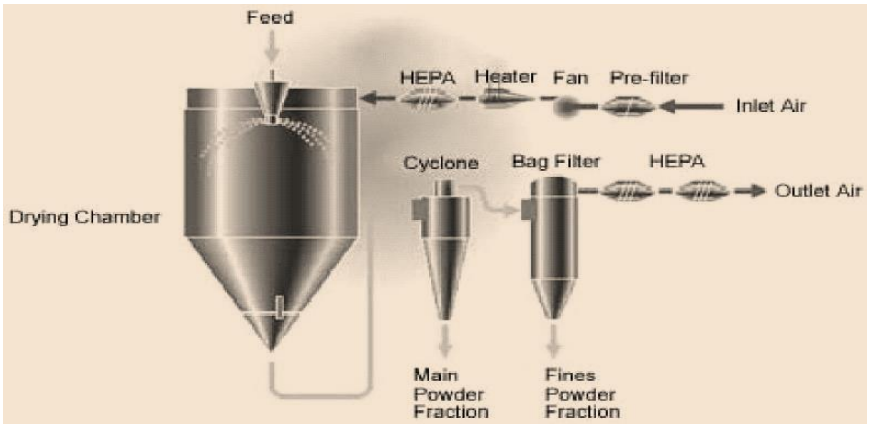

Figure 3: Diagrammatic representation of spray dryer.

4) **Micro-acidic environment:** As the solubility of the model drug is in acidic pH. Addition of pH modulating agents cause increase in the solubility of the drug (Herbrink *et al.*, 2018).

5) **Formulation with crystalline inhibitor:** Formulating drug with crystalline inhibitors can cause increase in the solubility by resisting the drug to converting into crystalline form from amorphous (Inam *et al.*, 2018).

Analytical Method Development:

Ultraviolet-Visible (UV/VIS) Spectroscopy

UV-Vis Spectrophotometry is mainly used for quantitative analysis. It also serves as a useful auxiliary tool for structural elucidation of various drugs to obtain specific information on chromophoric part of the molecules in solution (Ambasana, Kapuriya & Ladva, 2014). It deals with the measurement of energy absorbed when electrons are promoted from lower energy state to higher energy state (Mishra *et al.*, 2021).

Development and validation of a discriminatory dissolution method

Dissolution testing has emerged in the pharmaceutical field as a very important tool to characterize drug product performance. The significance of this test is based on the fact that the rate and extent of drug absorption depend on its dissolution from the dosage form. Therefore, dissolution test is used not only for quality control of the final dosage form, but also to assess several stages of formulation (Chaudhari & Kuchekar, 2018). Moreover, when an in vitro/in vivo correlation is demonstrated, dissolution can be used as a surrogate test to predict the in vivo bioavailability of pharmaceutical formulations.

RESEARCH GAP IDENTIFICATION

- BCS Class II and class IV drugs have poor solubility and affect dissolution, thereby affecting bioavailability.
- Poorly water-soluble drugs have a dissolution-rate limited oral bioavailability.
- Drug solubility and membrane permeability are the two factors affecting drug absorption from the GIT.
- Solubility enhancement is done to improve the drug solubility and increase bioavailability.
- Some of the major techniques used for increasing the solubility are Micronization, Salt formation, pH modification, modification in Crystal habit, drug dispersion in carriers, inclusion complexes, surfactant addition, etc.
- Drug dispersion in carriers: Eutectic mixtures, Solid dispersions, and Liquid solutions.

OBJECTIVES

The research aims to formulate and evaluate drug product formulation with improve invitro profile of poorly water-soluble Tyrosine Kinase Inhibitor using QbD approach.

The solid Dispersion is to be prepared using Hot Melt Extrusion technology, incorporating QbD elements in the formulation.

1. To enhance the drug solubility for improving the in-vitro drug release profile using different approaches such as solid dispersion, inclusion complex, or any other approach.
2. To perform a comparison for evaluating the different solubility enhancement techniques.
3. To adopt and finalize the best possible and economical approach for the solubility enhancement
4. *Optimization* of the developed Formulation using DoE.
5. *Characterization* of the developed formulation of a poorly water-soluble Tyrosine Kinase Inhibitor.
6. *In-vitro evaluation* of the developed formulation of a poorly water-soluble Tyrosine Kinase Inhibitor
7. *To establish IVIVC (in-vivo or ex-vivo) evaluation* of the developed formulation of a poorly water-soluble Tyrosine Kinase Inhibitor.

PROPOSED METHODOLOGY

The research aims to formulate a drug product with improved solubility

- Pre-formulation studies
- Analytical method Development
- Solid dispersion after selection of suitable method:
  - Selection of Polymers
  - Selection of Plasticizers
  - Selection of solvent
  - Screening of Polymers and Plasticizers
  - Drug-Polymer Compatibility Study
  - Study of Drug-Polymer Miscibility
  - Screening Batches using the DoE approach

- Characterization and optimization of the Solid Dispersion based on polymer and level of polymer.
- Solubility determination.
- Characterization of Final Solid Dispersion formulation
- Charge the formulation for Stability Study of the Final Formulation.
- In-vitro evaluation (Solubility and dissolution) of Final Solid Dispersion formulation.

- Other possible solubility enhancement techniques (Micronization, Spray drying, pH adjustment etc.).
- Comparison between the different techniques for solubility enhancement.
- Excipient selection and compatibility
- Prototype formulation development
- Formulation optimization
- Characterization and evaluation of the final formulation.
- Stability studies
- In-vitro and in-vivo correlation establishment.

THESIS OUTLINE

Chapter 1: INTRODUCTION: In this chapter a basic introduction about the dosage forms and solubility is described. The basic techniques for solubility enhancement will be discussed and focused.

Chapter 2: LITERATURE REVIEW: This chapter includes the deep and vigorous literature search. Formulations, methods and other approaches will be investigated and compiled for the research work to be conducted.

Chapter 3: MATERIALS AND METHODS: Theoretical discussion, drug profile,
drug category, drug mechanism, physio-chemical properties, Pharmacokinetic profile, Excipient Profile, Pre-formulation Studies, API Characterization (Physical appearance, Particle size distribution, Solubility, Hygroscopicity, Melting Point, X-Ray Diffraction, Infrared spectroscopy, SEM), Selection of Polymer and Surfactant, Screening of Carrier (Polymer) based on Literature and experiments, Screening of Surfactant based on Literature and experiments, API-Excipient

Compatibility Studies, Formulation Studies, Evaluation (In-process parameters, Development and Validation of a UV-Spectrophotometric Method, Solubility Studies, Dissolution, Assay, Microscopy, X-Ray Diffraction, Infrared Spectroscopy) to be discussed in this chapter.

Chapter 4: RESULTS AND DISCUSSION: Results and data interpretation to detailed discussed in this chapter along with the discussion.

Chapter 5: SUMMARY AND CONCLUSION: The results-based conclusion and summary to be explained in this chapter.

Chapter 6: REFERENCES: The references used in the thesis are enlisted here.

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CERTIFICATE
(SYNOPSIS APPROVAL CERTIFICATE)

This is to certify that the Synopsis for Ph.D. Thesis titled, **"Formulation development, optimization, and evaluation of a drug product with a poorly water-soluble tyrosine kinase inhibitor"**, submitted by **Mr. Ramendu Mishra** to the Career Point University, Hamirpur (H.P.), India in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY** in the Division/Department of Pharmaceutics, School of Pharmaceutical and Health Sciences has been approved by the Research Advisory Committee (RAC) after an Oral Examination of the student on dated 24-12-2022.

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